**REMARKS**

Applicants' attorney thanks Examiner Gibbs and SPE McGarry for the careful consideration given this case and the courteous interview extended to the undersigned on January 15, 2007. Claims 1-31 have been withdrawn from further consideration. New claims 78-87 have been added. Support for such new claims may be found at, for example, paragraphs [0108] to [0111] of the instant specification. Claims 60-74 have been canceled in an effort to focus attention on the subject matter being pursued in pending claims 32-59 and 75-87 and to expedite prosecution of the present application.

35 U.S.C. § 112, first paragraph- "Written Description"

During the interview, the rejection of claims 32-77 under 35 U.S.C. § 112, first paragraph because they purportedly fail to comply with the written description requirement was discussed. As set forth in the interview summary, the Examiner agreed that this rejection should be withdrawn in light of the amendment to the claims in the Response dated August 14, 2006 focusing the claims on inhibition of human ICAM-1 mRNA. Accordingly, Applicants respectfully request this rejection be withdrawn.

35 U.S.C. § 112, first paragraph- "Enablement"

The rejection of claims 32-77 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement was also discussed during the interview. The Examiner has taken the position that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to make or use the claimed invention. Specifically, the Examiner has stated that the specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the claimed methods *in vivo*. The Examiner argued further that that the efficacy of a compound *in vivo* based upon its performance *in vitro* is unpredictable. Applicants respectfully disagree.

Under 35 U.S.C. § 112, first paragraph, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, the specification must teach one skilled in the art how to practice the claimed methods. The test of enablement is whether one reasonably skilled in the art could make the and use the invention from the disclosures in the specification coupled with the information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). "The test is not merely quantititative, since a considerable amount of experimentation is permissible, if it is

merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

In the present application, the specification teaches how to choose target sites in human ICAM-1 (see, e.g., paragraphs [0048]-[0049]), the composition of the siRNA molecule (see e.g., paragraphs [0040]-[0047]), how to make an siRNA molecule (see, e.g., paragraphs [0054]-[0070]), how to measure its activity (see e.g., paragraphs [0071]-[0076]), how to use the siRNA molecule (see e.g., paragraphs [0077]-[0093]), how to specifically direct cleavage of ICAM-1 mRNA via RNA interference, including delivery methods and amounts (see e.g., paragraphs [0094]-[0121] and paragraphs [0123]-[0148]). Only routine experimentation would be required to make and use such siRNA molecules as presently claimed.

Applicants respectfully submit that independent claims 32 and 75 are directed to methods of administering such siRNA to a subject. Applicants respectfully submit that Applicant has provided a number of species of siRNA that target and inhibit expression of human ICAM-1 mRNA, as evidenced by the inhibition of human ICAM-1 expression in HEK 293 cells *in vitro*. Further, Applicants have provided sufficient guidance and description of the structural features necessary for obtaining a functional siRNA targeting human ICAM-1 mRNA, and have shown that such siRNA do in fact inhibit expression of the target mRNA upon administration. Moreover, as noted by the Examiner, Applicants did include prophetic examples 2-5 describing the *in vivo* administration of such siRNA and the predicted results, which is permitted pursuant to MPEP 608.01(p) to support the application and claims. The *in vitro* methods of inhibiting human ICAM-1 expression (i.e., Example 1), which demonstrate the efficacy or ability of the siRNA to silence human ICAM-1 mRNA upon administration to the cell, in combination with the general state of the art with respect to the *in vivo* delivery of siRNA, and the prophetic examples of the specification provide sufficient guidance to enable one ordinarily skilled in the art to use the claimed administration methods *in vivo*. Specifically, Applicants provided more than sufficient guidance with respect to, for example, treatment of diabetic retinopathy with siRNA directed to ICAM-1 *in vivo* (Example 2), treatment of VEGF-induced vascular permeability and leukostasis with siRNA directed to ICAM-1 *in vivo* (Example 3), treatment of neovascularization with siRNA directed to ICAM-1 *in vivo* (Example 4), and treatment of choroidal neovascularization with siRNA directed to ICAM-1 *in vivo* (Example 5).

Accordingly, as was discussed during the interview, the rejection under 35 U.S.C. § 112 for lack of enablement is inappropriate and should be withdrawn.

## CONCLUSION

Applicants have timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,

By: _____
Raymond A. Miller
Reg. No. 42,891

Dated: February 26, 2007
PEPPER HAMILTON LLP
500 Grant Street
One Mellon Bank Center, 50th Floor
Pittsburgh, PA 15219
(412) 454-5813
(412) 281-0717 - facsimile